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Fever of unknown origin (FUO)

II. Diagnostic procedures in a prospective multicenter study of 167 patients

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Introduction

The diagnostic workup of patients with fever of unknown origin (FUO) remains a challenge despite the variety of diagnostic methods currently available and many studies on the subject (1, 2, 7, 9, 14, 17, 18, 21, 25, 28, 30, 32, 40, 41, 46, 51). FUO has been defined by Petersdorf and Beeson (40) as a febrile illness of more than 3 weeks' duration, fever of 38.3 °C (101 °F) or higher on at least 3 occasions, and uncertain diagnosis after 1 week of in-hospital diagnostic workup. Recently, this definition has been modernized by excluding immunocompromised patients like patients with neutropenia or acquired immunodeficiency syndrome (AIDS) (12).

Because a large number of diseases have been reported to cause FUO, it is difficult to construct

algorithms covering the complete spectrum of FUO. Some attempts have been made in the past to outline diagnostic approaches (13, 16, 19, 26, 31, 38, 50); although they are of value, it is impossible to extrapolate these algorithms to the individual patient with FUO. Many relevant questions remain when studying these algorithms. Should one perform all examinations mentioned in the staged protocol in patients without potentially diagnostic clues? What is the diagnostic yield of all these investigations under various circumstances? Which patients are at risk for a life-threatening disease? Is it possible to distinguish patients with benign fevers?

Based on data retrieved in a retrospective analysis of investigations performed in patients with FUO and a questionnaire on diagnostic techniques used in patients with FUO among Dutch internists, we developed a staged diagnostic protocol (9, 10). This protocol was used in a prospective study on FUO performed during a 2-year period in all university hospitals in the Netherlands, reported elsewhere in this journal (11). In this study, all investigations, the indications for these investigations, and the results were registered prospectively to recover their utility under various conditions.

Methods

In all 8 university hospitals in the Netherlands, all immunocompetent patients fulfilling criteria for FUO according to Petersdorf and Beeson (40) were enrolled in this study. By reviewing records of all patients with fever and by checking the records of all patients in whom blood cultures were ordered on internal medicine wards, we tried to prevent unintended selection bias.

After informed consent, patients were included in our FUO protocol, which consisted of a standardized coded history and a standardized thorough physical examination. A number of additional investigations (Table 1) had to be performed in the first week of examination if an explanatory diagnosis was not established. Much weight was given to the presence or absence of potentially diagnostic clues (PDCs), defined as all localizing signs, symptoms, and abnormalities potentially pointing toward a diagnosis, and the use of these PDCs in the diagnostic process. PDCs

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Abbreviations used in this article: ACE, angiotensin converting enzyme; AIDS, acquired immunodeficiency syndrome; ANCA, antineutrophil cytoplasmic antibody; BAL, bronchoalveolar lavage; CT, computed tomography; FUO, fever of unknown origin; Hb, hemoglobin; In¹¹¹IgG, indium-111-labeled polyclonal immunoglobulin G; NIID, noninfectious inflammatory diseases; PDCs, potentially diagnostic clues; T4, thyroxine; TSH, thyroid stimulating hormone.

TABLE 1. Diagnostic protocol

Obligatory investigations performed in all patients

Sedimentation rate; hemoglobin; mean cellular volume; platelet count; leukocyte count and differential count; serum urea nitrogen; creatinine; sodium; potassium; protein; protein fractions; alkaline phosphatase; aminotransferase; lactate dehydrogenase; creatine phosphokinase; antinuclear antibodies; rheumatoid factors; urinary analysis; feces for occult blood; blood cultures aerobic and anaerobic (n = 3); tuberculin test; urine, feces, and sputum culture when indicated; chest X-ray; ultrasonography of upper abdomen

Phase 1 diagnostic protocol in patients without PDCs (n = 5) or with misleading PDCs only (n = 38)

Pulse/rectal temperature measurement by observer; fundoscopy by an ophthalmologist; calcium, phosphate, urate, amylase, and TSH/T4; immunoelectrophoresis of serum and urine; CRP; ACE; ANCA; anti-dsDNA; ASO; cryoglobulin; C3, C4, CH50; serology for Cytomegalovirus, Epstein-Barr virus, *Mycoplasma*, *Brucella*, *Toxoplasma*, *Borrelia*, *Coxiella*, *Treponema*, *Yersinia*; blood cultures incubating > 1 week; blood cultures, gastric fluid, urine cultures for tuberculosis; stools for worms, eggs, cysts; bone marrow puncture and culture for *Mycobacteria*, *Brucella*, *Yersinia*; In-111-IgG scintigraphy; X-Ray of sinus and teeth; ultrasonography of pelvis

Phase 2 diagnostic protocol in patients without PDCs

(Performed when Phase 1 did not reveal PDCs or diagnosis)
Hepatitis B serology; anergy tests; repeated chest X-ray; IgD in serum; liver biopsy and culture for *Mycobacteria* and other bacteria and fungi; crista biopsy and culture for *Mycobacteria*, *Brucella*, and common bacteria; echocardiography; CT of abdomen and chest; X-Ray colon; temporal artery biopsy in patients over 55 years

Abbreviations: TSH = thyroid-stimulating hormone; T4 = thyroxine; CRP = C-reactive peptide; ACE = angiotensin-converting enzyme; ANCA = antineutrophil cytoplasmic autoantibodies; dsDNA = double-stranded deoxyribonucleic acid; ASO = antistreptolysin O test; C = complement; CH50 = total hemolytic complement; In-111-IgG = indium-111-labeled polyclonal human immunoglobulin G; CT = computed tomography; PDCs = potentially diagnostic clues.

derived from history, physical examination, and additional investigations had to be registered in the protocol form. Based on these PDCs a differential diagnosis had to be made by the attending physician and registered in the protocol form. Based on this differential diagnosis, appropriate investigations were ordered to exclude or confirm these diagnoses in patients with PDCs. The indication to perform such investigations, and the entity thus searched for, had to be registered also. In the absence of PDCs and in patients with only misleading PDCs, patients underwent a staged standardized diagnostic protocol (see Table 1). Some tests were done as screening procedures in the absence of specific PDCs, before referral to the university hospital, or as a violation of the protocol by the attending physician. These were coded and studied also. Misleading PDCs are PDCs eventually not leading to the diagnosis. Helpful PDCs are PDCs eventually leading to the diagnosis.

Patients did not have to remain admitted; after inclusion, all investigations of the protocol could be performed on an outpatient basis. The clinical condition of the patient was the major reason for a longer stay in the hospital.

The standardized diagnostic protocol ended 1) when a definite diagnosis was made, 2) when PDCs appeared during the diagnos-

tic process, 3) when empiric treatment was started, or 4) when fever subsided. The final diagnosis was established by the attending physician and the first author. Diagnoses were established by serology, culture and histology preferably, but sometimes by exclusion of other diseases or response to therapy and disease course.

Follow-up was performed by analysis of the records of the patients and by telephone calls with attending physicians and individual patients; the last follow-up was performed in March 1996 for all patients with uncertain or no diagnosis.

In this study, periodic fever was defined as at least 2 episodes of fever, with intervals of at least 48 hours without fever.

Results of investigations were coded as normal or abnormal. Abnormal tests were subdivided as true positive (directly contributing to the diagnosis), false positive (misleading), or equivocal (abnormal but not providing any convincing evidence or not leading to the cause of FUO). Normal tests were coded as true negative or false negative. Because a gold standard for diagnostic accuracy was not available for many investigations, specificity and sensitivity could only be calculated assuming that negative results were true negative when further investigation or the final diagnosis did not contradict these results. The indications for the investigations were registered and coded also.

Most investigations were performed in each university hospital by the locally standard applied method, because the scale of this study did not allow us to centralize these measurements and investigations. However, all immunoblots for *Yersinia enterocolitica* were performed by the Department of Medical Microbiology, University Hospital Nijmegen (22, 24, 48). Interpretation of the immunoblot was as follows:

IgA negative and IgG positive for at least 2 bands: infection in the past that was considered equivocal.

IgA positive for at least 1 band and IgG positive for at least 2 bands: recent or persistent infection; this was considered a positive test.

IgA positive for 1 band and IgG positive for 1 band or IgA and IgG weakly positive for 1 or more bands: infection in past or beginning infection, repeat necessary; when unchanged this result was considered equivocal.

All other microbiologic serology was considered positive only when a fourfold elevation of IgG titer was present. When IgM was present but no fourfold elevation could be demonstrated, the test was considered equivocal.

Statistical analysis: Comparisons between groups were performed with the Fisher exact test (for the 2 × 2 tables) and the Mann-Whitney U test. P values of .05 or less were considered significant, NS is an abbreviation for nonsignificant. Logistic regression was applied to select variables that might predict whether a diagnosis would be made or not. Variables admitted in this analysis were most obligatory investigations (sedimentation rate, hemoglobin, mean cellular volume, platelet count, leukocyte and differential count, serum urea nitrogen, creatinine, sodium, potassium, protein, protein fractions, alkaline phosphatase, aminotransferase, lactate dehydrogenase, urinary analysis, antinuclear antibodies, blood cultures, Chest X-ray, and abdominal ultrasound), fever pattern, referral pattern, specific or nonspecific history and physical examination, age, sex, and the presence of night sweats. For the 8 university hospitals, 7 dummy variables were introduced. Logistic regression could be applied only to those patients who had "known" values for all

admitted variables. In patients with known values for the selected variables, but with missing values for 1 or more of the other admitted variables, it was verified whether the regression equation was valid. We calculated sensitivity and specificity with 95% confidence intervals.

Results

Of 167 patients meeting the criteria for FUO during the 2-year study period, a diagnosis could be made in only 117. In 43 (26%) patients, infections were found; in 21 (13%), neoplasms; in 40 (24%) patients, noninfectious inflammatory diseases (NIID) (11). A total of 10,855 investigations in 167 patients was performed.

Utility of the screening diagnostic protocol

All data on history and physical examination were entered in a database. The most common PDCs (present in more than 10 patients) were the following (number of patients in parentheses): relevant diseases in past (131), relevant operation in past (68), headache (62), myalgia (58), diarrhea (50), vertigo (48), arthralgia (48), changed bowel habits (42), nausea (42), heart murmur (41), pulmonary abnormalities (38), back pain (38), sore throat (37), abdominal complaints (37), dysuria (30), sensory dysfunction (28), arthritis (27), hepatomegaly (26), palpable breast abnormalities (22), contact with tuberculosis (21), visual complaints (21), tropical trip in recent past (21), goiter (20), splenomegaly (17), cold intolerance (17), neurologic abnormalities (17), insect bite (15), jaundice in past (15), dental intervention (15), hearing loss (15), heat intolerance (15), cervical lymphadenopathy (13), buccal aphthae (13), genital infection in past (12), generalized lymphadenopathy (11), and abnormal vaginal discharge (10). Other PDCs were found by various laboratory and imaging investigations in the first week of admission.

After 1 week of admission, PDCs were present in 162 (97%) patients (Table 2, Figure 1). A diagnosis

was made in 114 of 162 (70%) patients with PDCs and in 3 of 5 (60%) patients without PDCs (Fisher exact test, NS). In 16 patients without PDCs or with only misleading PDCs, a diagnosis was made (Table 3). Not every patient without PDCs or with only misleading PDCs underwent the complete first phase of the diagnostic protocol. Some investigations were not performed because new PDCs appeared or fever subsided. Forty-three patients completed the first phase; 15 of them also completed the second part. Exact data on the number of investigations performed as a screening procedure in the absence of PDCs can be found in Tables 4 and 5.

Utility of investigations in the diagnostic process

Chemical investigations: The obligatory chemical tests (see Table 1) were done in more than 95% of all patients except for serum protein fractions (145 patients), fecal occult blood (109 patients), and creatine phosphokinase (135 patients). None of the chemical investigations revealed the diagnosis, although some contributed somewhat to the diagnosis: in 1 patient with hyponatremia, meningitis proved to be the cause of FUO. In 4 patients with elevated urea, further investigations revealed mixed cryoglobulinemia ($n = 2$), systemic lupus erythematosus ($n = 1$), and pyelonephritis with ureteral obstruction ($n = 1$) as cause of the fever. In 6 patients with abnormal liver chemistry, abnormalities in the liver explaining the FUO were found (localization of malignant lymphoma and Hodgkin lymphoma, cytomegalovirus ($n = 2$), hepatitis C, and liver metastasis of adenocarcinoma). However, in 50% of our patients with FUO, nonspecific disturbances of liver chemistry were found. Fecal occult blood never was helpful in our patient group and was false positive in 10% of cases. In 1 patient, hypercalcemia led to the diagnosis of bone metastasis of breast cancer. Urate was elevated in 1 patient in whom gout presented as FUO. Creatine phosphokinase was elevated in 2 patients (with relapse polymyositis and dermatomyositis with interstitial lung fibrosis, respectively) and false positive in 1 patient, in whom a dental infection was the cause of FUO. Anemia, present in 127 patients, was normocytic in most patients. In 37 patients mean cellular volume (MCV) was abnormal; none of the 17 patients with microcytic anemia had gastrointestinal abnormalities responsible for the fever.

Immunologic serology (see Table 4): Antinuclear antibodies were helpful in establishing the diagnosis of systemic lupus erythematosus ($n = 2$), relapse of mixed cryoglobulinemia, and relapse of polymyositis. The presence of rheumatoid factors was helpful in establishing diagnoses for relapse of

TABLE 2. Potentially diagnostic clues* (PDCs) in 167 patients with fever of unknown origin

	Patients With Diagnosis ($n = 117$)	Patients Without Diagnosis ($n = 50$)		Total
		Spontaneous Recovery ($n = 37$)	Persistent Fever ($n = 13$)	
Helpful PDCs only	53			53
Misleading and helpful PDCs	48			48
Misleading PDCs only	13	35	13	61
No PDCs	3	2	0	5

*Defined in Methods section.

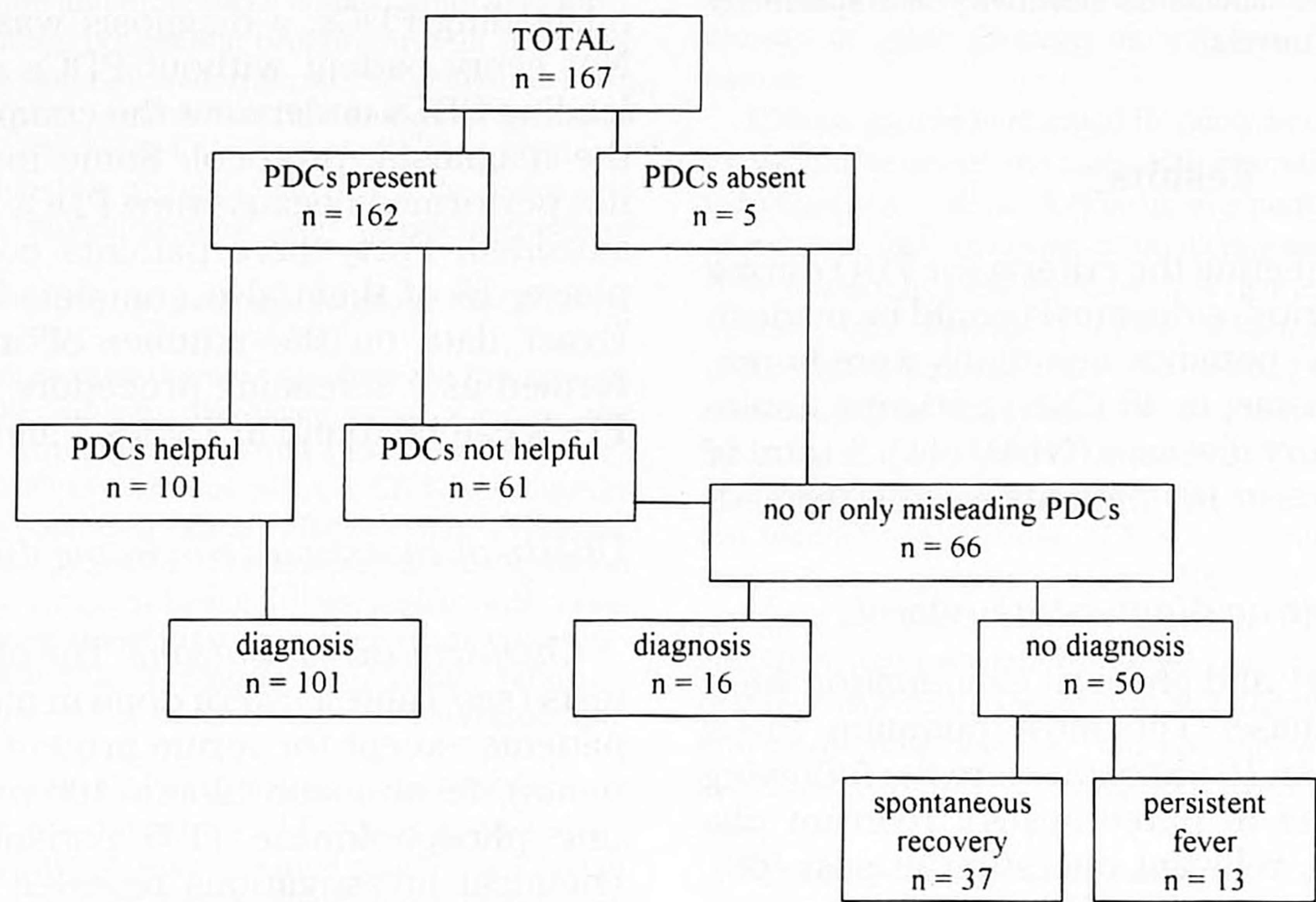


FIG. 1. Diagnostic workup of 167 patients with fever of unknown origin. PDCs = potentially diagnostic clues.

TABLE 3. Diagnoses in 16 patients with no PDCs or with only misleading PDCs

	Final Diagnosis*	Decisive Diagnostic Procedure
No PDCs (n = 3)	Bacterial endocarditis	Blood cultures not performed; without antibiotics in the referring hospital
	Polyarteritis nodosa	Fundoscopy†
	Mixed cryoglobulinemia	Cryoglobulin positive†
Misleading PDCs (n = 13)	Polyangiitis overlap syndrome	CT of thorax (revealed aneurysms)†
	Temporal arteritis (n = 3)	Temporal biopsy†
	Chronic yersiniosis (n = 2)	Positive serology; reaction therapy†
	Dental root infection	Radiography of teeth†, defervescence after extraction
	Hodgkin disease	Bone marrow biopsy†
	Factitious fever (n = 2)	Search for fraudulence
	Drug fever (n = 3)	Exclusion of other causes; after cessation of defervescence therapy

*N = 1 unless otherwise specified.
†Investigation performed in accordance with the diagnostic protocol.

TABLE 4. Diagnostic utility of immunologic and microbiologic serology and culture techniques

Investigation	No. of Patients (+PDCs/-PDCs)	Patients with PDCs No. (%)		Patients without PDCs No. (%)	
		TP	FP	TP	FP
ANA*	145 (30/115)	2 (7)	4 (13)	2 (2)	17 (15)
Rf*	124 (26/98)	1 (4)	1 (4)	1 (1)	1 (1)
IEF of serum*	105 (16/89)	1 (6)	3 (19)	2 (2)	2 (2)
ACE*	90 (14/76)	1 (7)	3 (21)	0	5 (7)
ANCA*	98 (10/88)	1 (10)	2 (20)	2 (2)	6 (7)
Anti-dsDNA	89 (16/73)	2 (13)	0	0	2 (3)
Cryoglobulin	68 (6/62)	3 (50)	0	2 (3)	0
Anti-ENA	62 (26/36)	2 (8)	0	0	0
Complement profile	95 (13/82)	0	0	0	0
ASO test	78 (9/69)	0	0	0	0
<i>Y. enterocolitica</i> immunoblot*	117 (9/108)	0	1 (10)	3 (3)	11 (10)
Blood cultures	167 (87/80)	6 (7)	0	2 (3)	2 (3)
Fecal cultures	92 (37/55)	0	0	0	0
Sputum cultures	51 (38/13)	4 (10)	3 (8)	0	0
PPD skin test	83 (21/62)	2 (10)	0	0	0

Abbreviations: ACE = angiotensin converting enzyme; ANA = antinuclear antibodies; ANCA = antineutrophil cytoplasmic antibody; anti-dsDNA = antibody to double-stranded DNA; ASO = anti-streptolysin O; ENA = extractable nuclear antigen; TP = true positive; FP = false positive; IEF = immunoelectrophoresis; PDCs = potentially diagnostic clues; Rf = rheumatoid factors; *Y* = *Yersinia*; PPD = purified protein derivative.

*See Results for detailed information.

polymyositis, relapse of mixed cryoglobulinemia, and vasculitis in rheumatoid arthritis. Immunoelectrophoresis of the serum was helpful in establishing diagnoses for relapse of mixed cryoglobulinemia, Schnitzler disease, and gamma-heavy chain disease. In 1 patient with abnormalities on the chest X-ray, angiotensin converting enzyme (ACE) was helpful in finding sarcoidosis. In 1 patient with histologically proven sarcoidosis, ACE was false negative. Antineutrophil cytoplasmic antibody (ANCA) helped establish the diagnoses for polyarteritis nodosa ($n = 1$) and Wegener disease ($n = 2$). ANCA was false positive in patients with the following final diagnoses: relapse of cryoglobulinemia, ulcerative colitis, lung empyema with *Actinomyces spp.*, hypersensitivity vasculitis, chronic pyelonephritis in ureter obstruction, sarcoidosis, and in 2 patients without diagnoses who recovered spontaneously without signs of vasculitis.

Endocrine investigations: In 1 patient who had diarrhea and weight loss, thyroid stimulating hormone (TSH) and thyroxine (T4) measurements proved the diagnosis of hyperthyroidism. In 4 patients, TSH was downregulated but hyperthyroidism was excluded by further testing. Diagnoses in these 4 patients were recurrent urinary tract infections, chronic pseudomonas infection of the lungs, hypersensitivity vasculitis, and no diagnosis, respectively. Plasma cortisol ($n = 16$), carcino-embryogenic antigen ($n = 11$), and α -fetoprotein ($n = 16$) did not help in finding diagnoses.

Microbiologic serology (see Table 4): In all patients with cytomegalovirus infection, atypical lymphocytosis was present. The following serology did not help in establishing diagnoses in this study: Epstein-Barr virus ($n = 92$), *Mycoplasma pneumoniae* ($n = 99$), *Brucella spp.* ($n = 73$), *Toxoplasma gondii* ($n = 85$), *Borrelia burgdorferi* ($n = 72$), *Coxiella burnetii* ($n = 78$), *Chlamydia psittaci* ($n = 62$), human immunodeficiency virus (HIV) ($n = 38$), influenza virus ($n = 44$), *Leptospira spp.* ($n = 12$), respiratory syncytial virus ($n = 36$), and rubella virus ($n = 11$). In 1 of 56 patients, serology for parainfluenza virus was positive. This patient also had right-sided heart failure and no other cause for the fever could be found; she recovered without specific therapy within 5 weeks. In 1 of 19 patients, a positive Widal test for *Salmonella typhi* was helpful in establishing the diagnosis, although cultures (blood, stools, urine) remained negative after empirically started antibiotics before admission to the hospital. Because of the clinical picture and course we concluded that she did have typhoid fever.

In 117 patients, serology for *Yersinia enterocolitica* was performed using the immunoblotting technique as described in the Methods section. Serology was negative in 57 patients, equivocal in 44 patients, and positive in 15 patients. The test was considered true positive in 3 of the 15 patients with positive serology: after 6 weeks of treatment with ciprofloxacin, their fever resolved, serology became negative, and no other cause for the fever could be found. After a follow-up of more than 3 years, these 3 patients remained afebrile. In 12 patients the test was consid-

ered false positive; treatment of more than 6 weeks with doxycycline and ciprofloxacin had no effect on the fever, and, in most of the 12, other causes for fever were found: malignant lymphoma ($n = 2$), right adnexitis, urinary tract infection, relapse of rheumatoid arthritis, mixed cryoglobulinemia, nonclassifiable granulomatous myositis, factitious fever, sarcoidosis, and no diagnosis ($n = 3$). Overall sensitivity and specificity were 100% and 89%, respectively (confidence intervals: 0.29–1.0 and 0.82–0.94, respectively).

Culture techniques (see Table 4): Aerobic and anaerobic blood cultures, obligatory investigations in our diagnostic protocol, were performed in all patients. In 8 (5%) patients these cultures contributed more or less to establishing the diagnosis: endocarditis in 2 patients, abscesses in 3 patients, an infected central venous device, *Pseudomonas spp.* bacteremia in pneumonia, and diverticulitis. In 19 patients false positive blood cultures were found growing coagulase-negative staphylococci ($n = 10$), *Streptococcus viridans* ($n = 3$), *Mycobacterium kansasii*, *Corynebacterium spp.*, *Propionibacterium spp.*, an anaerobic Gram-negative rod, an aerobic sporulating rod, and *Enterobacter cloacae* combined with *Bacillus spp.* (1 patient each). Blood cultures from a patient with ischemic colitis as a later complication and stomach cancer as cause of FUO grew *Bacteroides fragilis*; we consider these results equivocal.

Urinary cultures ($n = 134$) were helpful in establishing the diagnosis in 5 patients. None of the 69 patients with a normal urinary sediment turned out to have a urinary infection. In 5 patients the test was considered false positive. After treating the assumed urinary tract infection adequately, bacteriuria disappeared, whereas the fever remained unchanged. In 24 patients bacteriuria was found with less than 10^5 microorganisms/mL; there were no signs of a urinary tract infection in any of them.

Fecal cultures for *Salmonella spp.*, *Campylobacter jejuni*, *Shigella spp.*, and *Yersinia enterocolitica* were performed in 92 patients; none of the cultures was positive. In 1 patient the clinical course combined with a positive Widal test suggested salmonellosis as cause of the FUO; cultures probably remained negative because of empirically started antibiotics before admission.

None of the cultures of blood, urine, and gastric fluid for *Mycobacterium tuberculosis* was positive, and none of the cultures for other microorganisms performed without PDCs in accordance with the diagnostic protocol contributed to the diagnosis.

Other cultures contributing to the diagnosis always were performed because PDCs were present for infection (that is, culture of liver biopsy in a patient with cryptococcal infection, cerebrospinal fluid in a patient with Spitz-Holter drain and hypona-

tremia, lymph node in a patient with tuberculous lymphoma, pleural fluid in a patient with actinomycosis, central line tip in a patient with infected central venous device, and pericardium biopsy in a patient with tuberculous pericarditis).

Imaging techniques (see Table 5): A chest X-ray helped to establish the following diagnoses in 6 patients without PDCs for chest diseases: Hodgkin disease, malignant lymphoma, recurrent pneumonia combined with urinary tract infection, disseminated cryptococcosis, systemic lupus erythematosus, and sarcoidosis. One patient with pleural empyema had a normal chest X-ray, but scintigraphic and computed tomography (CT) techniques revealed the diagnosis. Assuming all other chest X-rays to be true negative, we calculated overall sensitivity and specificity (see Table 5).

Upper abdominal ultrasonography was performed in only 158 of 167 patients because an abdominal CT had already been performed in 9 patients before inclusion or referral to the university hospital. Upper abdominal ultrasonography contributed to the following diagnoses: malignant lymphoma, liver abscess and pelvic abscess (2 patients each), angioimmunoblastic lymphoma, gamma-heavy chain disease, sarcoidosis, right-sided heart failure, systemic lupus erythematosus in a patient with enlarged kidneys and abnormal ultrasound reflections, liver metastasis (seen on second ultrasonography), chronic pyelonephritis in ureter obstruction, and tuberculous pericarditis. Abnormal findings were seen on ultrasonography in 68 patients, but in 12 (8%) patients the findings led to unnecessary investigations and thus were considered false positive. In 3 patients ultrasonography was considered false negative because abdominal CT revealed the diagnosis.

Abdominal CT was helpful in making the diagnosis in 2 patients without PDCs (that is, pericarditis due to vasculitis in rheumatoid arthritis and malignant lymphoma, respectively). In 14 patients abdominal CT was considered false positive because it led to unnecessary investigations like laparoscopy, puncture of suspected lesions, or laparotomy. Abdominal causes for the fever were not found in any of the patients with a normal abdominal CT. Considering these CT to be true negative, we calculated overall sensitivity and specificity (see Table 5).

In 3 patients without PDCs, a chest CT enabled us to diagnose tuberculous pericarditis, malignant lymphoma, and dermatomyositis with interstitial lung fibrosis, respectively. In 1 patient, the chest CT was normal, but shortly thereafter an enlarged axillary lymph node became palpable, which turned out to be a lymph node metastasis of a previously treated larynx carcinoma.

Transthoracic echocardiography was useful in

TABLE 5. Diagnostic utility of imaging techniques and histologic investigations

Investigation	No. of Patients (+PDCs/-PDCs)	Patients with PDCs		Patients without PDCs		Overall Sensitivity % (CI)	Overall Specificity % (CI)
		TP	FP	TP	FP		
Chest X-ray*	167 (51/116)	12 [†]	4	6 [†]	2	95 (73-99)	96 (91-98)
Abdominal US*	158 (47/111)	7	5	6	7	81 (54-96)	92 (85-96)
Pelvic US	28 (9/19)	2	2	0	2	100 (16-100)	85 (65-96)
X-ray, sinuses	82 (19/63)	0	4	0	4	NC	NC
X-ray, teeth	47 (6/41)	0	0	1	0	NC	NC
Abdominal CT*	84 (51/34)	12 [†]	10	2 [†]	4	100 (77-100)	80 (69-89)
Chest CT*	45 (30/15)	12	4	3	1	94 (70-99)	83 (64-94)
Heart US*	66 (33/33)	6 [†]	3	0 [†]	2	86 (42-98)	92 (81-97)
X-ray, colon*	29 (16/13)	3	2	0	3	100 (30-100)	81 (61-93)
X-ray, ileum*	24 (16/8)	0	1	0	0	NC	NC
In ¹¹¹ IgG scan	58 (35/23)	9 [†]	5	0 [†]	3	48 (24-71)	80 (63-91)
Ga-67 scan	27 (5/22)	1	1	1	9	100 (16-100)	60 (39-79)
Bone scan*	28 (17/11)	4	6	0	6	80 (29-97)	48 (27-70)
BM aspiration*	74 (40/34)	1	2	0	0	14 (2-58)	97 (90-100)
Liver biopsy*	34 (25/9)	2	0	1	0	75 (20-96)	100 (88-100)
BM biopsy*	49 (23/26)	5	1	4	2	NC	NC
Temporal biopsy	26 (7/19)	2	0	2	0	NC	NC
Enteric biopsy	13 (7/6)	1	0	0	0	NC	NC
Skin biopsy*	25 (23/2)	3	1	0	0	NC	NC
Skin-muscle biopsy*	29 (17/12)	6 [†]	1	0 [†]	0	NC	NC
Colonic biopsy	11 (11/0)	1	0	0	0	NC	NC

Abbreviations: BM = bone marrow; CI = confidence interval; CT = computed tomography; FP = false positive; Ga-67 = Gallium-67; In¹¹¹IgG = Indium-111-labeled immunoglobulin G; NC = not calculated; PDCs = potentially diagnostic clues; TP = true positive; US = ultrasonography; X-ray = radiography.

*See Results for detailed information.

[†]Statistically significant by the Fisher exact test.

finding the following diagnoses in 6 patients with PDCs for cardiac disease: endocarditis (n = 2), pericardium infiltration in acute leukemia, mitral and tricuspid valve disease in heart failure, pericarditis due to vasculitis in rheumatoid arthritis, and tuberculous pericarditis. In 1 patient with endocarditis proven at autopsy, echocardiography was negative several times.

X-ray of the colon helped to find the following diagnoses in 3 patients with PDCs: colonic polyp in *Streptococcus bovis* endocarditis, diverticulitis, and diverticulitis causing multiple hepatic abscesses.

X-ray series of the small bowel (n = 24) did not contribute to the diagnosis in this study. Abnormal pictures (nodular ileitis not consistent with Crohn disease) were found in 1 patient with positive *Yersinia enterocolitica* serology. Prolonged courses of antibiotics did not cure this patient, and he still suffers from periodic fever.

Imaging techniques that were helpful in finding the diagnosis (only in patients with PDCs) were the following: 2 of 19 brain CTs, showing infarction in 2 patients with endocarditis; CT of thoracic spine showing lesions of Hodgkin disease; intravenous pyelography showing obstruction of the left ureter in pelvic abscess; 1 of 10 mammograms showing a lesion that proved to be cancer; 2 of 13 Doppler ultrasound studies showing venous thrombosis and a lesion that turned out to be T-cell lymphoma.

Scintigraphic techniques (see Table 5): Results of the indium-111-labeled polyclonal immunoglobulin G (In¹¹¹IgG) scintigraphy are described extensively elsewhere (8) (see Table 5). Other scintigraphic methods like In¹¹¹-leukocyte scintigraphy (performed in 16 patients) and Technetium-99m-leukocyte scintigraphy (8 patients) were all performed in patients without PDCs for local inflammation or infection and did not help establish a diagnosis. In 6 patients, positive scans were found but after extensive further investigations, no local inflammation could be confirmed. An infection was found only in 2 of 17 patients with negative scans.

Gallium-67 scintigraphy was performed in 27 patients (see Table 5). A localized inflammation was not found in any of the 15 patients with negative scans. Considering these scans to be true negative, we calculated overall sensitivity and specificity.

A bone scintigraphy helped to find the following diagnoses in 4 patients with PDCs for local inflammation: Hodgkin disease (n = 2), Still disease (showing arthritis), and bone metastasis of breast cancer. In 1 patient with endocarditis and osteomyelitis caused by *Staphylococcus aureus*, bone scintigraphy was false negative.

Histologic investigations (see Table 5): Bone marrow aspiration helped to establish the diagnosis in 1 patient with acute monocytic leukemia. This patient

had an extreme left shift in the peripheral blood, and 2 previous bone marrow aspirations were not conclusive. In 2 patients, bone marrow cytology was false positive. In the first patient, myelodysplastic syndrome was suspected in the first aspiration, but after spontaneous recovery, this could not be confirmed. He has been afebrile for more than 3 years now, and a diagnosis has never been established. In the other patient, myelodysplastic syndrome was suspected but at autopsy, culture-negative endocarditis was found. In 6 patients bone marrow aspiration did not yield specific abnormalities, whereas bone marrow biopsy was helpful in establishing the diagnosis; considering these tests as false negative, and the remaining tests as true negative, we calculated overall sensitivity and specificity (see Table 5).

Liver biopsy was helpful in finding the diagnosis in 3 (9%) patients. In 1 patient without PDCs for liver disease, liver biopsy helped establish the diagnosis of granulomatous hepatitis. No underlying disease was found, and after therapy with corticosteroids, his condition improved in several months, without recurrence for 4 years now. In 1 patient with disturbed liver chemistry only, liver biopsy was helpful in finding the diagnosis of disseminated cryptococcal infection. In a third patient with abnormal liver chemistry, ultrasonography of the upper abdomen was normal in the first week of admission. A second ultrasonography showed a large lesion in the liver, a biopsy of which revealed adenocarcinoma. In 22 patients, liver biopsy showed nonspecific abnormalities only. In 1 patient a blind liver biopsy was false negative, showing nonspecific abnormalities only, whereas histology of biopsies at laparoscopy showed granulomatous hepatitis.

Bone marrow biopsy aided in the diagnosis in 9 (18%) patients. In 4 patients without PDCs for blood disorders or lymphadenopathy, the diagnoses malignant lymphoma and Hodgkin disease (2 patients each) were found with the help of bone marrow biopsy. In 3 patients with peripheral blood smear abnormalities (leukopenia in 2, extreme left shift in 1), biopsy established the following diagnoses: Hodgkin disease, acute myelofibrosis, and acute monocytic leukemia. Bone marrow biopsy in 1 patient with hot spots on a bone scintigraphy established the diagnosis of metastasis of an adenocarcinoma of the breast. The fifth patient had generalized lymphadenopathy, and bone marrow biopsy pointed to the diagnosis of angioimmunoblastic lymphoma, which was confirmed by a third lymph node biopsy. In 3 patients the results were false positive. In 1 patient, bone marrow biopsy suggested myelodysplastic syndrome, but a repeated biopsy could not confirm this. Eventually, temporal arteritis proved to be the cause of the fever. In 1 patient the bone biopsy showed features

of malignant lymphoma, but the patient recovered spontaneously and a second bone biopsy was completely normal. She has been afebrile for 3 years now. In a third patient, Hodgkin disease was suspected from bone marrow biopsy, but after revision the diagnosis was sarcoidosis. Since in 3 of 37 patients with normal bone marrow biopsies, disorders that could have involved the bone marrow (angioimmunoblastic lymphoma, Hodgkin disease, and gamma-heavy chain disease) were found eventually by other means, the possibility exists that the results were false negative. It therefore seems hazardous to give figures for sensitivity and specificity.

Bronchoalveolar lavage (BAL) was performed in 21 patients for cytologic and microbiologic investigations, 19 of whom had abnormal chest radiographs. In 1 patient only, BAL established the diagnosis. This patient had culture-negative pleural empyema; histologic examination of the BAL fluid showed *Actinomyces* colonies. After a 6-week treatment with penicillin, fever and symptoms subsided.

In 25 patients a skin biopsy was performed, including 2 patients without skin lesions. In 3 patients with skin lesions, the procedure helped to find the following diagnoses: urticarial vasculitis, hypersensitivity vasculitis, and erythema nodosum in the context of tuberculous axillary lymphoma. In 15 patients, nonspecific abnormalities were found. In 1 patient, skin biopsy suggested septic embolism. Treatment with penicillin had no effect. Because of complaints of arthritis and urethritis with conjunctivitis and moderate response to salicylate, the presumed diagnosis was Reiter disease. The patient's complaints disappeared completely after 8 months, and 3 years later no other cause for the fever has been found.

Biopsy of skin and muscle was performed in 17 patients with PDCs (skin diseases or abnormal electromyography) (see Table 5). In 1 patient with abnormal electromyography, histologic examination of the biopsy material revealed lymphocytic arteritis; the patient recovered spontaneously after 1 month without a diagnosis being made. He has been free of disease for more than 4.5 years now.

In 24 patients, enlarged lymph nodes were removed for histologic and microbiologic investigations; this procedure helped to establish the diagnosis in 12 (50%) of them. No pathologic lymph nodes were present at physical examination upon admission in 5 of these 12 patients, but in 11 of these 12 patients, generalized lymphadenopathy was demonstrated after extensive ultrasonographic and radiographic investigations. Lymph node biopsies were not helpful in establishing the diagnosis if lymphadenopathy was confined to the cervical or inguinal region ($n = 8$). In the case of generalized lymphadenopathy, biopsy was helpful in 11 of 14 patients (Fisher exact test, $p = .001$).

In 3 of 4 patients with urine abnormalities, renal biopsy was helpful (Wegener disease, systemic lupus erythematosus, mixed cryoglobulinemia with glomerulonephritis).

A lumbar puncture was performed in 11 patients; in 2 as a screening procedure without any PDCs, implying a violation of the diagnostic protocol. In 2 (18%) patients this technique was helpful in finding the diagnosis; both patients had severe headache but no signs of meningitis. In these patients a sterile mononuclear infiltrate of the cerebrospinal fluid was found, and in 1 patient biopsy of the meninges was negative. The presumable diagnosis of Mollaret meningitis was established in both by exclusion of other diseases.

In 5 patients, splenectomy was part of the diagnostic workup before referral because splenomegaly was found; it led to the diagnosis in 2 patients. In the first patient, there was a discrepancy between the histology of the bone marrow biopsy and that of the spleen; the diagnosis remained uncertain until generalized lymphadenopathy developed and lymph node histology was done which showed angioimmunoblastic lymphadenopathy with dysproteinemia (AILD). In the second patient, bone marrow biopsy was suspect for Hodgkin disease but proof could be found only by spleen histology.

Other successful histologic investigations performed because PDCs were present were articular puncture ($n = 3$) proving pseudogout in 1 patient, gastroscopy ($n = 11$) with gastric biopsy proving 1 case of stomach cancer, pleural puncture ($n = 13$) pointing to systemic lupus erythematosus in 1 patient, and pericardial puncture ($n = 1$) in 1 patient proving tuberculous pericarditis.

Predictors of likelihood of reaching a diagnosis

Univariate analysis (Table 6): For all parameters and PDCs, the value of predicting the likelihood of reaching a diagnosis was established with help of univariate analysis. Parameters that were significantly different between patients with a final diagnosis and patients without a diagnosis are listed in Table 6. Of all specific and nonspecific PDCs in the history and physical examination, only night sweats reached statistical significance. There was also no significant difference between the 2 groups concerning sex, presence of PDCs, use of the screening diagnostic protocol, age, duration of fever, referral pattern, and fever pattern (continuous versus discontinuous).

Logistic regression of prediction of possible diagnosis (Table 7): All values of the variables admitted in logistic regression were known in 92 patients. After stepwise selection, 3 variables remained in the

logistic regression model: serum protein electrophoresis (1 = normal, 2 = abnormal), periodic fever (1 = 1 period, 2 = more than 1 period) and hemoglobin (Hb) (1 = normal, 2 = abnormal). In an additional 53 patients the values of serum protein electrophoresis, periodic fever, and Hb were known, while some of the other admitted variables had missing values. With the regression coefficients (1.83, -1.43, 1.21, respectively) and an intercept of -2.70, we estimated the probability of finding a diagnosis.

Discussion

In this study, we prospectively evaluated the utility of diagnostic techniques used in patients with FUO. In a retrospective study on FUO (9), we found that the use of diagnostic techniques was abundant, whereas in many cases the exact indication for the investigation could not be retrieved. The present study allows us to draw conclusions on the overall diagnostic value of many of these techniques, and by prospective registration of PDCs, estimate the screening diagnostic value of many of these techniques.

The merit of chemical investigations is mainly to direct the physician to the possible location of disease, making a more selective search possible; only rarely do these investigations lead directly to the diagnosis. In this study, 50% of the patients were found to have nonspecific liver disturbances, but in only 6 (4%) patients were specific liver diseases the cause of FUO. Thus, finding such disturbances is relatively meaningless. This is in agreement with data from ear-

TABLE 6. Significantly different parameters in patients with and without diagnosis*

Parameter (No. of Patients)	No Diagnosis ($n = 50$) No. (%)	Diagnosis ($n = 117$) No. (%)
Elevated ESR (164)	38 (76)	104 (90)
Abnormal Hb (167)	29 (58)	98 (84)
Abnormal sodium (164)	5 (10)	32 (28)
Lowered serum protein (151)	9 (19)	41 (39)
Abnormal protein electrophoresis (145)	29 (63)	92 (93)
Abnormal ASAT (167)	10 (20)	45 (39)
Proteinuria (151)	6 (14)	36 (33)
Night sweats (140)	40 (91)	70 (75)
Periodic fever (167)	28 (56)	28 (24)
Hospitalization ≤ 21 days	26 (52)	34 (20)
Median hospitalization in days (range)	19 (7-83)	34 (7-295)

Abbreviations: ESR = erythrocyte sedimentation rate; Hb = hemoglobin; ASAT = aspartate aminotransferase.

*Using univariate analysis.

TABLE 7. Classification of patients with known values of variables and those with some missing values

Serum Protein Electrophoresis	Periodic Fever (periods)	Hemoglobin	Patients with Known Values		Patients with Missing Values		EPD
			Diagnosis		Diagnosis		
			Yes	No	Yes	No	
Normal	1	Normal	1	1	0	1	.25
		Abnormal	3	2	2	2	.53
	> 1	Normal	0	6	1	2	.07
		Abnormal	0	2	0	1	.21
Abnormal	1	Normal	5	3	4	2	.68
		Abnormal	38	6	21	2	.88
	> 1	Normal	2	3	4	2	.33
		Abnormal	13	7	5	4	.63

Abbreviations: EPD = estimated probability of diagnosis from logistic regression in patients with known value.

lier studies (23, 34) showing that abnormal liver tests in FUO are not predictive of a diagnostic liver biopsy.

The diagnostic yield of immunologic serology is also relatively low. Although antinuclear antibodies, rheumatoid factors, ACE, ANCA, antibody to dsDNA, and extractable nuclear antigen sometimes contributed to the diagnosis, these tests are more often false positive and are of little use without PDCs pointing to specific immunologic disorders. Mixed cryoglobulinemia turned out to be a rather common cause of FUO, even in patients without specific PDCs and underlying disorders. Thus, this investigation seems worthwhile even in patients without PDCs.

In the literature, atypical subacute thyroiditis (42) and other masked thyroid diseases (44, 45) appear as a cause of FUO. Most of the patients reported did not have overt thyrotoxicosis but had some features of thyroid disease such as weight loss despite a good appetite and frequent bowel movements. This finding was confirmed in our series. It can be concluded that the diagnostic yield of thyroid testing without the presence of any PDCs for thyroid disease is very low.

In all published series on FUO, infections are the most common cause of FUO. The screening value of microbiologic serology in patients without PDCs has never been studied before in patients with FUO. In our series of patients without PDCs for infection, the diagnostic yield of these tests appears to be very low. Such investigations should not be used as screening procedures early in the diagnostic process for patients without PDCs for specific infections. Serology for cytomegalovirus infection appears to be helpful only in patients with PDCs for cytomegalovirus infection (for example, atypical lymphocytosis), as previously described (32, 40). A relatively new technique used in this series is Western blot serology for *Yersinia enterocolitica*. Although occasionally helpful, its low specificity seems to limit the use in this group of patients.

The diagnostic yield of imaging procedures is often difficult to establish because the yield of these tech-

niques depends on other investigations performed already. In our study we tried to avoid this problem by including a chest radiography and abdominal ultrasonography in the first obligatory part of the diagnostic protocol and by dividing the protocol into 2 stages. When there were pulmonary complaints or abnormalities at physical examination, the chest radiography was very useful, but even in patients without pulmonary disorders this simple technique was of use sometimes.

We included abdominal ultrasonography as an obligatory test in all included patients with FUO. Extrapolation of data presented by comparative studies on abdominal ultrasound and CT in the patient with FUO is hazardous. Only 1 study (33) tried to minimize systemic bias as to the type of examination performed last (the diagnostic yield of techniques is dependent on the techniques already used), by scheduling patients so that each examination was performed first in roughly one-third of patients. In this study it was found that the 2 modalities have a similar ability to detect local inflammation. We had several reasons for choosing ultrasonography instead of CT as an obligatory test: the relatively low cost, no radiation burden, little discomfort for the patient. In a substantial proportion of patients, upper abdominal ultrasonography was useful, and we feel this test should remain obligatory in the diagnostic workup of all patients with FUO. However, we should keep in mind that in a considerable proportion of patients, upper abdominal ultrasonography was false positive and led to unnecessary investigations. Ultrasonography of the pelvis was not useful in patients without PDCs and led to unnecessary investigations in some patients. When negative in a patient with prolonged fever, the abdominal ultrasonography has to be supplemented by abdominal CT in a later phase, which has a very high sensitivity. One has to be careful, however, not to overinterpret CT data because of the relatively low specificity. Unnecessary and invasive diagnostic procedures may be ini-

tiated. Sensitivity and specificity of abdominal and chest CT appear to be similar; the latter has not been studied previously in patients with FUO.

Not much is known about the value of echocardiography in patients with FUO. Our results show that in patients with more than 3 weeks of fever, the technique was useful only in patients with PDCs for cardiac abnormalities (that is, heart murmur, friction rub, or chest pain) and that it is not an appropriate technique to use early in the diagnostic process when such PDCs are absent.

Scintigraphic techniques were useful only in patients with PDCs for local inflammation or infection, as we have extensively discussed elsewhere (8). These techniques were useless as screening procedures in our population of patients.

Radiologic evaluation of the gastrointestinal tract can be valuable if performed in the proper setting. In our study it never was useful as a screening procedure, and we believe it should not be used as a screening procedure in patients without abdominal PDCs. Even in the presence of microcytic anemia, abnormalities of the gastrointestinal tract were not responsible for the FUO in our series.

We used X-rays of the sinuses as a screening procedure, as advised by others (16, 38, 39, 43). The diagnostic yield was very low, and, in many patients, false positive findings led to unnecessary investigations.

Bone marrow aspiration was of little use in the absence of PDCs for a bone marrow disorder. Thus, as a screening procedure this technique is of little use, and anemia alone is certainly not a reason to perform this investigation in patients with FUO.

The diagnostic yield of liver biopsy in patients with FUO has been studied extensively in the past. It is likely that selected groups of patients with PDCs for liver abnormalities were studied. In our study, liver biopsy was part of the second stage of the screening diagnostic protocol and was performed in 9 patients without PDCs for liver abnormalities, yielding 1 case of unexplained granulomatous hepatitis. We are aware of the discussion whether the descriptive diagnosis "granulomatous hepatitis" is a real diagnosis or should be put in the "no diagnosis" group (30). In order not to conceal this interesting group of patients even though the causal relationship between granulomatous hepatitis and FUO is not clear, and, in most cases, the entity is secondary to a vast variety of diseases (15, 20), we did not classify this condition in the "no diagnosis" group. We feel that liver biopsy in the absence of PDCs may be of some use in a later stage of the diagnostic workup.

In our population of patients with FUO, bone marrow biopsy had a relatively high diagnostic yield when performed in a later stage of the diagnostic process, even in the absence of PDCs. We are not

aware of other studies investigating the screening value of this technique.

Because temporal arteritis is an important cause of FUO in patients older than 50 years (30), we included temporal biopsy as a screening procedure in a later stage of the diagnostic protocol in patients older than 55 years. Despite this rigorous search, temporal arteritis was found in only 2 patients without PDCs and in 2 patients with typical complaints. Thus, in our study the diagnostic yield was not as high as in that of Knockaert and colleagues (30), who found temporal arteritis in 15% of the cases. In a late stage of workup and before starting empirical corticosteroids, it is justified to perform such a biopsy.

The role of the BAL in patients with FUO has not been elucidated. Although in most patients undergoing BAL, chest radiography was abnormal, the diagnostic yield was very low. Selection of patients was probably the most important reason for this low utility. The technique is used early in the diagnostic process of lung abnormalities, and patients in whom the procedure is useful will probably not classify as FUO.

In this study the screening value of small-intestinal biopsy was nil. It was also of little value in patients with abdominal complaints, probably because Crohn and Whipple disease and coeliac disease were not found in our series. We feel it should not be used as a screening procedure early in the diagnostic process.

Skin and skin-muscle biopsy had a diagnostic yield of 35% in our series, only when performed in patients with skin abnormalities and/or abnormal electromyography. Other studies on polyarteritis nodosa (PAN), systemic necrotizing vasculitis, and FUO (6, 35, 49) also showed that skin-muscle biopsy is useful only in suspect skin or muscle areas.

In our population, if lymphadenopathy was confined to the cervical or inguinal region (with negative X-ray of chest and abdominal ultrasound), lymph node biopsy was not helpful in establishing the diagnosis, in contrast to patients with generalized lymphadenopathy in whom it had a high yield.

Unlike in the study of Knockaert (30), blood cultures were still helpful in establishing the diagnosis of endocarditis in 2 of our patients. In both patients blood cultures became positive after the patient stopped taking empirically started antibiotics, an aspect already emphasized by others (3, 25, 40).

It can be concluded from our series that cultures of urine, of sputum, and from other specific sites were useful only in patients with PDCs pointing to those sites. By performing screening cultures the risk of confusion with false-positive cultures is greater than the diagnostic yield.

Tuberculin skin testing was positive in 2 patients who turned out to have active tuberculosis; in a third

patient with tuberculosis, a skin test was not performed. In none of the other patients was a positive purified protein derivative (PPD) found, reflecting the low prevalence of tuberculosis in our country. In other series tuberculin testing did not perform so well because of the high rates of false negative tests in patients with active tuberculosis (up to 25%) (37) and high rates of positive tests without active disease in certain subgroups like elderly patients (5) and immigrants from developing countries (47).

The importance of PDCs has been emphasized in many reviews of FUO. The attending physician is advised to observe the Sutton Law: "to go where the money is" (4, 13, 27, 36, 50). The value of PDCs has not been evaluated systematically before. Two retrospective studies showed significantly lower chances of reaching a diagnosis when no PDCs were present (9, 51). This was not confirmed in the present study, in which we prospectively registered and used PDCs and found that the presence of PDCs does not increase the likelihood of reaching a diagnosis. Because of the low percentage of patients without PDCs, these findings have to be interpreted carefully: we have no doubt that the search for PDCs remains the most important tool for the doctor to find the cause of FUO, but our study demonstrates that many of these PDCs are misleading and do not lead to a diagnosis. In univariate and logistic regression analysis of patients with and without a diagnosis, we found significant differences only for periodic or intermittent fever, erythrocyte sedimentation rate (ESR), and hemoglobin, in accordance with Knockaert (29). The chances of finding a diagnosis is significantly higher in patients with continuous fever, high ESR, and low hemoglobin. It is interesting to see that other PDCs and parameters, such as hepatosplenomegaly, age, duration of fever, the existence of PDCs, and the use of the screening diagnostic protocol, did not influence the likelihood of finding a diagnosis.

It was surprising that our diagnostic protocol was of use in 26% of the patients to whom it was applied. Indeed, this figure seems high, but when we look at the investigations that really are of diagnostic value when used as screening procedure, only a few should be used that way: temporal artery biopsy in patients older than 55 years, fundoscopy, sophisticated serology for *Yersinia enterocolitica*, serum for cryoglobulinemia in an early stage, and bone biopsy and abdominal and chest CT in a later stage of the diagnostic process. This means that the screening diagnostic protocol can be limited rigorously in the absence of PDCs.

Ordering investigations as screening procedures in the hope (mostly vain) that something abnormal will come up has many disadvantages, like possible adverse reactions or complications, loss of faith of the patient, staggering costs of testing, and—perhaps

most important—a soporific effect on the doctor's diagnostic mental activities. Repeating a thorough history-taking, physical examination, and obligatory investigations and waiting for PDCs to appear probably is better than ordering more screening investigations in the hope that something abnormal will come up. Supportive treatment with nonsteroidal anti-inflammatory drugs (NSAIDs) can be helpful at this stage. Only rarely do patients deteriorate while using NSAIDs without presenting new PDCs. In these rare patients, further diagnostic workup should be performed or a therapeutic trial with, for example, antibiotics, steroids, or antituberculous agents started.

Summary

From January 1992 until January 1994, we used a standardized diagnostic protocol for the 167 immunocompetent patients with fever of unknown origin (FUO) admitted on the internal medicine wards in all 8 university hospitals in the Netherlands. This protocol consisted of a standardized coded history and standardized physical examination for all 167 patients. A number of additional obligatory investigations had to be performed in the first week of admission for all patients, and all potentially diagnostic clues (PDCs) thus retrieved had to be registered. In the presence of PDCs, specific investigations had to be performed based on the differential diagnosis. In the absence of PDCs or in the presence of only misleading PDCs, patients underwent a screening 2-staged diagnostic protocol.

In 162 (97%) patients, PDCs were present after 1 week of admission. In 61 patients these PDCs were all misleading. The likelihood of reaching a diagnosis in patients with PDCs was not significantly higher than that in patients without PDCs, probably because of the high proportion of misleading PDCs. The likelihood of establishing a diagnosis was significantly lower (<10%) only for patients with recurrent fever, normal erythrocyte sedimentation rate (ESR), and normal hemoglobin. All other PDCs were not significantly different in patients with a diagnosis compared with patients without a diagnosis.

The screening 2-staged diagnostic protocol proved useful in 10 of 43 patients in whom it was used. The screening value of immunologic and microbiologic serology and endocrine investigations was nil; these investigations probably should be performed only when PDCs for the disease searched for are present. Scintigraphic techniques, echocardiography, and other imaging procedures were never helpful in our population in the absence of PDCs. Many patients with FUO had nonspecific anemia and disturbed liver chemistry. In the presence of these findings alone, without other more specific PDCs, the likelihood of

reaching a diagnosis with help of bone marrow aspiration was nil, and with help of liver biopsy, it was low. Enteric biopsy was never helpful. If lymphadenopathy was confined to the cervical or inguinal region (with negative chest X-ray and abdominal ultrasound), lymph node biopsy was not helpful, in contrast to patients having generalized lymphadenopathy, in whom the technique had a yield of 79%.

As shown in this study, the search for PDCs remains an important tool for establishing the diagnosis in patients with FUO, although in many cases these PDCs appear to be misleading. Directed diagnostic workup—using the PDCs retrieved by repeated, meticulous history taking and physical examination—remains the most efficient and intellectually satisfactory way to solve the problem of FUO in the individual patient. A standard protocol in patients with FUO in whom the obligatory investigations, as used by us, do not lead to the diagnosis can be limited to the tests that proved to be of some use as screening procedure: temporal biopsy in patients older than 55 years; fundoscopy; serology (Western blot) for *Yersinia enterocolitica*; serum for cryoglobulin at an early stage of the diagnostic process; and bone biopsy, liver biopsy, abdominal computed tomography (CT), and chest CT at a later stage. Repeating a thorough history-taking, physical examination, and obligatory investigations and waiting for PDCs to appear probably is better than ordering more screening investigations in the hope that something abnormal will come up. Supportive treatment with nonsteroidal anti-inflammatory drugs (NSAIDs) can be helpful at this stage. Only rarely do patients deteriorate while using NSAIDs without presenting new PDCs. In these rare patients, further diagnostic workup should be performed or a therapeutic trial with, for example, antibiotics, steroids, or antituberculous agents started.

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